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Dr. Yuan-Yuan Chiu
U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research (CDER)

Dear Dr. Yuan-Yuan Chiu,

The National Research Institute of Chinese Medicine, Taiwan, has been working in the area of botanical drug development for the past 40 years. At present we have a staff of 100 , housed in a modern and well-equipped facility with a total area of 250,000 square feet. Our past activities have been on the isolation and identification of pure active natural compounds, with the intention of developing them into prescription drugs. However, during the last few years, it became clear to us that a more appropriate approach may be the development of botanical extracts (mixtures) into drugs. However, one main problem is the lack of clear guideline from regulatory authorities on botanical drug development. Therefore, the guidance document entitled "Guidance for Industry Botanical Drug Products" from your office is induced a most welcome publication. It serves to delineate a possible path for researchers and industry to follow for botanical drug development and commercialization. This document further shows the appreciation of the valuable experience of historical use of botanical drugs and the difference between them and synthetic drugs. For the first time, meaningful botanical drugs can now be available to the consumers. It may create an interesting and new paradigm in medicine.

As researchers, we are, however, very much aware of some intrinsic problems in the whole area of botanical drug development. As most of the proposed botanical drugs have to be prepared from natural sources which can be highly variable, how to assure

meaningful batch-to-batch consistency in the product throughout its testing and final production is a serious concern. Chemical fingerprinting can provide chemical characterization. However, it is our experience that preparations may be functionally variable even though the chemical profile seems rather uniform. There are therefore two questions that should be seriously considered.

1. What criteria should be used to determine batch-to-batch consistency of botanical drug preparations? Should it be:

   a. chemical fingerprinting alone;
   b. chemical fingerprinting as one biological (used related) assay; or
   c. chemical fingerprinting plus pharmacological fingerprinting?

   Logically (c) is the only way as it clearly defines the composition and functional uniformity of preparations. It is perhaps the best way at this time to provide assurance of product quality and consumer protection.

2. When should such batch-to-batch consistency be established? It should be in place at the earliest stage of drug development so that one can have confidence on the data from pre-clinical and clinical studies. Data from such preparations are truly representative of the product. Without the assurance of consistency in such preparations, data from all the studies are not comparable and rather meaningless.

The document so far touches on such issues indirectly. It is our feeling that the document should clearly reflect this problem and suggest guidelines to provide solution.

As researchers in this field, we deeply appreciate the document you produced. We look forward to hearing its further developments.

Sincerely,

Chen Chieh-fu
Director, NRICM